Response to Comment on: Schuit et al. β-Cell–Specific Gene Repression: A Mechanism to Protect Against Inappropriate or Maladjusted Insulin Secretion? Diabetes 2012;61:969–975

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Thank you for the invitation to respond to the comment by Rutter and Pullen (1). We are aware of the original work by the Rutter laboratory on *LDHA* and *MCT1* (2,3) and cited it before (4) and in the Perspective (5). However, with the limitation of 50 references in the Perspective, some original research could not be cited, and we apologize for that.

We strongly disagree, however, with the claim from Rutter and Pullen to be the first to discover islet-specific gene repression through bioinformatic analysis (1). It should be made clear that until 2006 research on lactate dehydrogenase and moncarboxylate transporter 1 was conducted in order to understand how β-cells respond to glucose and other nutrients (2,3); there was no mention in these articles of the idea that genes could be selectively repressed in one cell type. Then, as well known to the islet research community, starting in 2006 with a Juvenile Diabetes Research Foundation program, our group followed a systematic genome-wide mRNA expression approach studying mouse islets ex vivo in comparison with a large reference tissue panel from the same animals in order to identify novel genes with islet-specific gene repression. For this we used two different mRNA expression platforms and a specially designed statistical approach in order to search for tissue-specific gene repression (4). In 2007, at a symposium organized by Rutter, we first introduced the biological concept of genes that are specifically repressed in islets (6). Furthermore, as tissue-specific repression of genes is a new concept in biology, our investigations went beyond the realm of pancreatic islets, and we studied the case of specific gene repression in the liver. Finally, we added mechanistic and tissue developmental dimensions to the study (4). All this was well known to Rutter, who had privileged access to some of our mouse mRNA expression data.

The claim is based on a limited study by Pullen et al. (7) that has severe methodological shortcomings (mRNA data from public databases of nine reference tissues is compared with islets prepared in the laboratory of the authors). In Table 1 of ref. 7, two of the top three most "islet-specifically" repressed genes (7) were hemoglobin α and β chains, which are of course abundantly present in erythrocytes. Instead of critically analyzing this as artifact of the loss of blood cells from islets during the standard collagenase isolation, the authors speculated about α and β globin genes being selectively silenced in β-cells: "This suggests that hemoglobin may play a more general role in oxygen balance within many cell types. Therefore, their specific absence from β-cells could affect the susceptibility of these cells to oxidative stress."

Ideally, science is a collaborative endeavor in which being the first has little relevance as compared with rigor of measurement and care of interpretation. In reality, science is often conducted by ambitious humans. Usually, constructive compromises between these two worlds exist, leading to healthy competition or fruitful collaboration and finally scientific truths.

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